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Attention Deficit/Hyperactivity Disorder

Pharmacotherapy

ABSTRACT

Pharmacotherapy, one of the effective modalities of treatment for attention deficit/hyperactivity disorder (ADHD), was discovered serendipitously and, until recently, consisted primarily of short-acting methylphenidate and dextroamphetamine compounds. The US Food and Drug Administration's (FDA) approval of Concerta in 2000 followed by approval of additional long-acting methylphenidate (Ritalin LA; Metadate CD) and amphetamine formulations (Adderall XR) expanded the repertoire. By providing sustained efficacy for most of the school day, mid-day administration is avoided, privacy is preserved, and adherence to treatment improves. In 2001, an isomer preparation of methylphenidate, Focalin, was approved, and in 2002, Strattera, a selective noradrenergic agent expanded treatment options to non-controlled agents. At this time, stimulant preparations continue to remain the first-line agents due to their unparalleled efficacy and safety record. However, current treatment remains empirical due to lack of scientific data guiding the choice of agent as well as dose.

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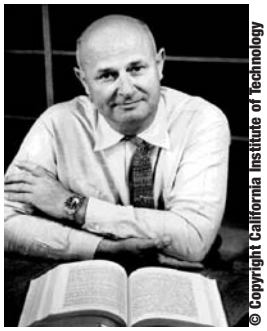
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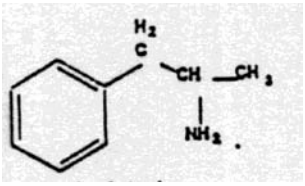
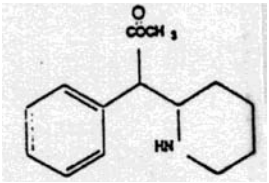
In 1927, Gordon Alles discovered increased alertness and decreased fatigue after self-administering ephedrine, an extract from the ephedra plant.

In 1932, Charles Bradley found that when Benzedrine was administered to children with nervous disorders a significant improvement in schoolwork occurred.



Benzedrine



Methylphenidate

INTRODUCTION

Pharmacotherapy for ADHD began in 1887 with the synthesis of amphetamine by L. Edeleano. In 1927, ephedrine, an extract from the ephedra plant used to treat asthma, was in short supply, and Gordon Alles, a British University of California Los Angeles (UCLA) graduate student, was given the task of synthesizing it. He didn't accomplish this, but in the process, self-administered some of the extract and discovered increased alertness and decreased fatigue.[1] He patented this extract of racemic amphetamine and in 1932 sold it to Smith Kline and French, who marketed it as Benzedrine for the treatment of asthma and nasal congestion.

In 1931, George Bradley opened the Emma Pendleton Bradley Home, now Bradley Hospital, to treat children with nervous disorders. In 1932, his great nephew, Charles Bradley, having finished his residency at Babies Hospital in New York, joined the staff.[2] The patients underwent extensive evaluations, including examination of cerebrospinal fluid that frequently resulted in headaches. Bradley experimented with Benzedrine with the hope of increasing the rate of cerebrospinal fluid production by the choroid plexus in order to minimize the headaches thought to result from fluid lost during the lumbar puncture.[3] Although the headaches did not improve, teachers noted significant improvement in schoolwork. Bradley tested these observations further and documented both behavioral[4] and academic improvement in children with a variety of neuropsychiatric manifestations,[5] and in 1950 he reported similar results for dextroamphetamine.[6]

METHYLPHENIDATE

Methylphenidate was synthesized by Panzion in 1944 as a cyclized derivative of amphetamine.[7] Mier replicated this synthesis in 1954, and the medication was marketed by Ciba-Geigy as a geriatric medication. Its similarity to d-amphetamine suggested its use in children with behavior disorders.

Methylphenidate is marketed as a 50:50 mixture of d-threo and l-threo enantiomers. Recent advances in stereospecific manufacturing have allowed commercial preparation of d-threo isomer, the pharmacologically active compound (l-threo being metabolized before reaching systemic circulation). Efficacy and safety have been tested in a double-blind study where improvement in teacher and parent ratings was found to last up to six hours. Adverse effect profile was similar to racemic formulations.[8]

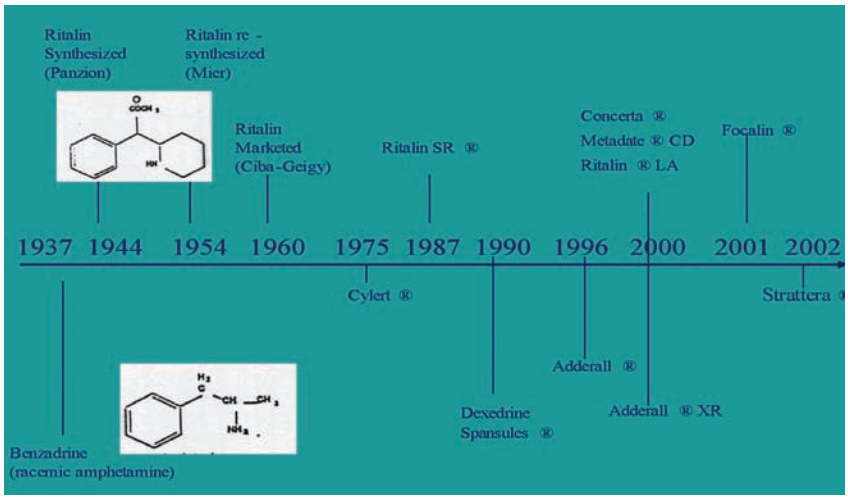
Four open studies[9–12] were followed by the first placebo-controlled study[13] in 1963 supporting its efficacy. In a 1968 *Journal of the American Medical Association* review article, Millichap[14] concluded that "methylphenidate is the drug of choice and amphetamine sulfate is the second most successful drug" based on a comparison of all reported cases treated with methylphenidate (337 patients; 84% improvement) and amphetamine (415 treated; 69% improvement) without considering any other issues, such as dosing, patient populations, or response measures. This misinterpretation persisted, and even the 1980 edition of Gilman's pharmacology text[15] endorses methylphenidate as being superior to amphetamine and the drug of choice for hyperkinetic children based on Millichap's conclusions. This misinterpretation, along with the marketing of Ritalin in pediatric journals, the wide use of methylphenidate in research studies in the 70s[16] and 80s,[17] and the misperception that methylphenidate was very different from dextroamphetamine, increased the acceptance of Ritalin as the drug of choice. Although placebo-controlled studies[18,19] and Barkley's 1977 review[16] (15 studies using amphetamines showed 74%

improvement;14 studies with methylphenidate showed 77% improvement) were published, the misperception persisted. Additional comparative studies showing similar efficacy and safety profiles[20–22] did little to reverse this trend until the FDA approval and the marketing of Adderall in 1996.

LONG-ACTING PREPARATIONS

The millennium ushered in the FDA's approval of several long-acting stimulant preparations. These can provide extended activity of 8 to 12 hours mimicking an either two or three times per day dosing regimen with their comparable immediate release agent. The extended release characteristics allow for once-daily dosing, therefore avoiding in-school drug administration.

Methylphenidate formulations. *Concerta.* Concerta, an extended release formulation of methylphenidate, is delivered in a tablet containing 78 percent of the medication within two separate inner compartments (each with a different concentration) and an outer coat containing 22 percent of the medication (e.g., 4mg in an 18mg capsule). A third inner compartment, composed of inactive ingredients, absorbs fluid from the gut through the semi-permeable capsular membrane, and its expansion results in drug release. The product was specifically designed to produce increasing concentration of medication in the bloodstream, which was determined necessary for behavioral efficacy.[23] The Concerta capsule is virtually tamper proof, minimizing potential abuse,[24] and the once-a-day dose, administered under parental supervision, also reduces potential for diversion. Efficacy and safety were established in clinical trials.[25] A 12-month follow-up of 289 children who had previously participated in these trials found the drug to be well tolerated.[26] Medication compliance was excellent but older age, inattentive subtype, and low starting dose predicted lower adherence.[27] Concerta is also effective in adolescents; however, in up to a third of the 220 subjects studied, a higher dose (72mg) was necessary to achieve benefits.[28] A follow-up study in adolescents has shown efficacy to persist for up to nine months.[29] A study comparing Concerta to short-acting formulations showed that it improved driving performance.[30]



The millennium ushered in the FDA's approval of several long-acting stimulant preparations.

Metadate CD. Metadate CD is a capsule containing beads that allow 30-percent immediate absorption of methylphenidate, while the remaining 70 percent is formulated for continuous absorption throughout the day. It provides efficacy for 8 to 9 hours.[31]

Ritalin. Ritalin LA also uses a bead technology to provide sustained efficacy up to 8 to 9 hours. Half of the beads are absorbed immediately while the remaining 50 percent are absorbed approximately four hours after administration.

All of these long-acting preparations are effective and have similar adverse effects. Comparative data is beginning to emerge that can provide some guidance to physicians when selecting the appropriate preparation. A within-subject study in 36 ADHD children showed improved attention and behavior with both Ritalin LA 20mg and Concerta (18mg and 36mg) but different response profiles, indicating slightly better effect from Ritalin LA during the first four hours post dose.[32]

Pharmacokinetic studies show Ritalin LA (20mg) provides more rapid absorption and higher peak plasma concentration than Concerta 18mg.[33] In a comparison study of Metadate CD and Concerta, behavioral and attentional measures showed greater improvement with Metadate CD during the first four hours post-dose, and were similar for both drugs between 5 and 8 hours post-dose. Concerta, however, was found to last longer and provide efficacy in the early evening.[31] Similar symptom control was achieved with higher Concerta doses and lower doses of Metadate CD during 1.5 to 6 hours post-dosing while the reverse was true 7.5 to 12 hours post dosing.[34]

Ritalin SR, the original wax-matrix sustained release tablet, was noted to have a delayed onset of action and variable efficacy.[35] Metadate ER and Methylin ER have similar limitations.

Amphetamine formulations. *Dexedrine Spansule.* Dexedrine Spansule is an extended-release preparation with an immediate release of an initial dose followed by gradual release of the remaining medication over a prolonged period. Maximum plasma concentration of dextroamphetamine after a 15mg dose occurred at eight hours.

TABLE 1. Long-acting ADHD agents

DRUG NAME	ACTIVE COMPOUND	DOSES	CORRESPONDING DOSE OF IMMEDIATE RELEASE VERSION	LENGTH OF EFFICACY	DRUG DELIVERY MECHANISM	IMMEDIATE/ SUSTAINED CONCENTRATION	MONTLHY COST
Concerta® (J & J)	Racemic methylphenidate HCL	18mg 27mg 36mg 54mg		12 hours	Osmotic capsule	22% is on outer coat and absorbed immediately; 78% is released continuously	$74.70
Metadate® CD (Celltech)	Racemic methylphenidate HC	10mg 20mg 30mg	5mg bid 10mg bid 15mg bid	8–9 hours	Beads	30% immediate; 70% continuous	$76.80
Ritalin® LA (Novartis)	Racemic methylphenidate HCL	10mg 20mg 30mg 40mg	10mg bid 15mg bid 20mg bid	8–9 hours	Beads	50% immediate; 50% 4 hours later	$68.40
Metadate® ER (Celltech)	Racemic methylphenidate HCL	10mg 20mg			Wax Matrix		$60.00
Methylin® ER (Mallinckrodt)	Racemic methylphenidate HCL	10mg 20mg			Wax Matrix		$62.40
Ritalin SR® (Novartis)	Racemic methylphenidate HCL	20mg			Wax Matrix		$68.40
Methylphenidate SR® (Geneva)	Racemic methylphenidate HCL	20mg					
Dexedrine® Spansules (Glaxo Smith Kline)	Dextroamphetamine Sulfate	5mg 10mg 15mg		8 hours			$64.80
Dextroamphetamine Sulfate Spansules (Generic)	Dextroamphetamine Sulfate	5mg 10mg 15mg					$49.81
Adderall XR® (Shire Inc.)	Neutral salts of dextroamphetamine with dextroamphetamine saccharate and d,l-amphetamine aspartate monohydrate extended release	5mg 10mg 15mg 20mg 25mg 30mg	2.5mg bid 5mg bid 10mg bid 15mg bid	12 hours	Beads	50% immediate; 50% 4 hours later	$73.20
Strattera® (Eli Lilly)	Selective Norepinephrine reuptake inhibitor	10mg 18mg 25mg 40mg 60mg					$90.00

Comparative studies[36–37] with immediate-release Ritalin, Adderall, dextroamphetamine sulfate, and pemoline show sustained efficacy.

Adderall XR. Adderall XR, an extended-release formulation of mixed amphetamine salt with a bimodal releasing pattern, mimics a twice-daily dosing schedule (20mg Adderall XR capsules is equivalent to Adderall 10mg bid). The gelatin capsule contains immediate-release pellets designed to release the first half of the dose immediately and delayed-release pellets designed to release the active medication 4 to 6 hours post dosing. Its safety and efficacy were established in a large placebo-controlled clinical trial.[38] A community-based study of nearly 3,000 ADHD children previously managed with psychostimulants confirmed that its long duration of action (up to 12 hours) and once daily dosing most likely improved both compliance and parent satisfaction.[39]

There are no comparative studies to guide physicians on choosing the appropriate preparation. Clinically, both of these preparations have similar profiles; however, there can be individual variability. A laboratory study has shown longer DA signaling with striatal Adderall application compared to dextroamphetamine and d-l amphetamine.[40] Comparative studies with Adderall and dextroam-

phetamine show comparable efficacy and tolerability for both agents. Activity level was lower on Adderall during first hour.[37] Teacher ratings were lower in the morning for Dexedrine Spansules compared to the immediate release agents,[37] but we do not know if the same occurs with Adderall XR.

Selective noradrenergic agents. *Strattera.* Strattera (atomoxetine), a specific presynaptic inhibitor of the norepinephrine transporter, is effective in children and adolescents with ADHD.[41–44] Parental reports indicate improved behavior lasting into evening hours despite a four-hour half-life suggesting that CNS effects may differ from plasma kinetics. Atomoxetine appears effective in ADHD without exacerbating tics in children with comorbid tic disorders.[45] Preliminary studies also support its efficacy in ADHD with comorbid symptoms of behavioral and affective nature.[46] Abrupt discontinuation of atomoxetine in children and adolescents did not lead to any significant discontinuation-emergent adverse events.[47] It increases dopamine in frontal cortex but not in nucleus acumens and striatum, suggesting an unlikely abuse potential.[48] Strattera, therefore, unlike the stimulants, is not classified as a controlled substance.

Strattera is effective, but how does it compare to the stimulants? In an analogue classroom comparison, teacher ratings showed improvement for a greater number of children on Adderall XR vs. atomoxetine, while parent ratings showed improvement for both medications but greater satisfaction with Adderall XR.[49] A differential response to stimulants and atomoxetine may occur in up to 35 percent.[50]

Cylert. Cylert, another long-acting agent marketed since 1975, is not widely used due to severe hepatotoxicity (13 reported cases of acute liver failure, 11 resulting in death or liver transplantation) occurring within four weeks of the onset of signs and symptoms of liver failure.[51]

Information on several ADHD medications is provided in Table 1.

ADVERSE EVENTS

All the extended release psychostimulants are associated with a similar side effect profile as their immediate release compounds. Of subjects taking Concerta, 6.9 percent discontinued participation in a 12-month study due to adverse effects including tics, appetite suppression, insomnia, worsening of ADHD, and hostility. Very infrequent cases of somnolence, abdominal pain, headache, compulsive skin picking, hypertension, emotional lability, hallucinations, and weight decrease also necessitated drug withdrawal.[26] Pooled data from several studies found incidence of tics for Concerta (4%) similar to placebo (3.7%).[52]

The effects of these medications on growth are less clear. A recent report of 24-month exposure to short-acting methylphenidate shows mild growth suppression (1cm/year in height and 1.25kg/year in weight).[53] These concerns have prompted prospective gathering of data with the introduction of the long-acting agents and some of the preliminary data is showing weight decrease during the first three months of Concerta use but then increased weight during the next nine months while height increased steadily by 5.2cm.[26] Atomoxetine is also associated with a modest initial slowing of growth velocity, followed by near-normal growth rates during a two-year exposure.[54] Because the cause of ADHD medication effects on growth and weight are not fully understood, continued monitoring throughout treatment is important.

Atomoxetine appears to be well tolerated for most children with six percent discontinuing due to adverse events, and common adverse events (decreased appetite, vomiting, dizziness, headaches) decreased during ongoing treatment. Modest blood pressure and pulse elevations have been found to remain stable.[55] Recent reports of a teenager and an adult treated with Strattera for several months who developed hepatotoxicity have resulted in FDA labeling changes, recommending discontinuation in patients who develop jaundice or laboratory evidence of liver injury.[56] It is not known whether these two patients were poor metabolizers (7% of the population are poor metabolizers of CYP2D6 substrates). Strattera has been marketed since 2002, and over two million patients have been treated. No liver problems were noted in the 6,000 participants in the clinical trials.

Interactions with food. Children who have difficulty swallowing pills can benefit from beaded preparations because they can be sprinkled on foods, such as applesauce,[57] and Methylin®, a short-acting methylphenidate agent, is available in chewable tablets. Metadate CD and Ritalin LA had a longer lag time until absorption when administered with a high fat meal. High fat breakfast meals also altered the absorption and pharmacokinetics of Adderall XR but not Concerta.[58] The clinical significance of these dietary effects is not known.

Costs. In the US market, costs for a month's supply of the long-acting agents vary from $64.80 for Dexedrine spansules to $90.00 for Strattera.[59] Long-acting agents are not always more expensive than their immediate release counterparts (Adderall XR- $73.20; Adderall $84.00). Generics are usually lower (generic amphetamine, $74.40; generic methylphenidate, $37.20; Ritalin, $54.00). The high cost of Strattera may also be offset by the cost of dispensing a non-controlled substance.

Pharmacogenetics. Genetic studies have identified several candidate genes (e.g., DAT1, DRD4, SNAP-25) affecting dopaminergic and noradrenergic transmission.[60]

TABLE 2. Animal model studies: ADHD candidate genes and medication response

ANIMAL MODEL	ACTIVITY LEVEL	METHYLPHENIDATE RESPONSE	DEXTROAMPHETAMINE RESPONSE	SSRI RESPONSE
Wild-Type[81]	Normal	Increased activity	Increased activity	No effect
DAT1 Knock-out mice[82]	Hyperactive	Decreased activity 30 min after drug exposure, which is dose dependent	Decreased activity 30 min after drug exposure, which is dose dependent[86]	Decreased activity
DRD4 Knock-out mice[83]	Reduced activity		Supersensitive to amphetamine	
SNAP-25 deletion (Coloboma mice)[84]	Hyperactive	Increased activity	Decreased activity	

Animal models developed to understand the role of these candidate genes are shedding some light on how ADHD medications work and at the same time also indicating a great deal of complexity that we have yet to grasp (Table 2).

Mice with the SNAP-25 deletion exhibit hyperactivity (3–10 times that of controls) that is decreased with d-amphetamine but not methylphenidate.[61] D-amphetamine and methylphenidate both act at pre-synaptic terminals and increase synaptic dopamine concentrations by different mechanisms. D-amphetamine reverses the dopamine transporter resulting in dopamine release[62–64] and is not inhibited by reserpine pretreatment, a drug that depletes vesicular stores of catecholamine.[65] Methylphenidate works primarily by blocking the dopamine transporter[64,65] and is ineffective without available dopamine. Response rates to the stimulants in ADHD children is remarkably high (up to 98% when both d-amphetamine and methylphenidate are tried in the same subjects); however, there is a preferential response to either one or the other of these two agents in about 80 percent of subjects[20,22] suggesting that genes, such as the SNAP-25, may be playing some role in drug response. In the Dopamine Transporter Knockout mice, both methylphenidate and d-amphetamine work; however, their effect, surprisingly, does not appear to be mediated by increased striatal dopamine but by the 5-HT system.[66] ADHD children have not been found to respond to serotonergic agents; however, we have not as yet identified and treated (-/-)DAT homozygous knockout individuals that could potentially have a similar response as the animal model. A study of an Irish ADHD sample[67] did report a favorable MPH response in individuals with over-expression of DAT while an African-American[68] and a Brazilian[69] sample found poor response. Preferential transmission of long allele of MAO[70] has been associated with favorable MPH response as well as DRD4-7 repeat.[71] See Table 3.

ADDITIONAL TREATMENTS

Additional agents used to treat ADHD that are not FDA approved include the alpha-2 agonists, such as clonidine,[72] and guanfacine, which has been shown to decrease ADHD symptoms.[73] Bupropion, an antidepressant with both dopamine and noradrenergic effects, has also been shown to have some ADHD efficacy in adults.[74–76]

AGENTS IN DEVELOPMENT

A methylphenidate transdermal patch (MTS) applied for 7 to 12 hours a day significantly improve ADHD and oppositional defiant disorder (ODD) symptoms. The patch was well tolerated and adverse effects were comparable to other methylphenidate preparations.[77] Patch removal terminates drug delivery but behavioral effects could persist for another hour or two as systemic methylphenidate is metabolized.

A phase II trial of a selegeline transdermal system showed significant improvement on standard ADHD rating scales in 18 ADHD male patients (ages 6–17). Tyramine restrictions were unnecessary because selegeline inhibits brain MAO-A and B activity without significant inhibition of gut MAO-A. Thus the probability of acute hypertensive reactions from dietary tyramine is reduced.[78]

Modafinil, a medication that acts selectively on hypothalamic areas that regulate wakefulness and activate the frontal cortex, used primarily to treat narcolepsy, significantly improved ADHD symptoms in a trial of 248 children.[79]

MARKET SHARE

Since their introduction in 2000, long-acting stimulant preparations have been replacing their short-acting counterparts. Data on the number of prescriptions for the last week of October, 2004, shows long-acting agents capturing 68.3 percent of market share.[80] Methylphenidate and dextroamphetamine compounds appear to

TABLE 3. ADHD linkage studies and drug rersponse

	CANDIDATE GENE	STUDY SAMPLE	DRUG RESPONSE	COMMENTS
Kirley, et al.[67]	DAT1 10- repeat	119 Irish children	Favorable MPH response	Retrospective measurements of MPH response
Winsberg and Comings[68]	DAT-10 repeat	African American children N=30	Poor MPH response	Open trial
Roman, et al.[69]	DAT-10 repeat	Brazilian Children N=20 without 10/10 N=30 with 10/10	Poor MPH response	Open trial
Tahir, et al.[71]	DRD4-7 repeat	104 triads	Favorable MPH response	Retrospective measurements of MPH response
Manor, et al.[70]	MAO (X chrom) Preferential transmission of long allele	133 triads	Commission errors on TOVA (CPT test) improved with MPH	

share the market reflecting scientific data that shows equal efficacy and tolerance for these two classes. Marketing factors may play a role in the amount of prescriptions written for specific agents within the methylphenidate classes (e.g., Concerta has greater market share than Ritalin LA or Metadate CD) and within the dextroamphetamine classes (e.g., Adderall XR has most of the market compared to Dexedrine Spansules). Generic preparations of both methylphenidate and dextroamphetamine agents predominate prescriptions for short-acting agents, suggesting that cost may be the key factor. See Figures 1 and 2.

CLINICAL PRACTICE GUIDELINES

Methylphenidate and dextroamphetamine compounds remain the first-line agents for ADHD. Over a hundred short-term and a few long-term studies[17,53] support efficacy and safety. Response rates are over 80 percent for each of these agents, most likely because they target numerous neurotransmitter systems. A trial of both methylphenidate and dextroamphetamine agents should be given to each individual to determine which one works best and has the least adverse effects. The clinical presentation of the individual child should guide the choice of the individual compounds (e.g., Metadate CD or Ritalin LA may provide better coverage right after taking the medication while Concerta may provide better coverage at the end of the day). Dosing can also be adjusted to the clinical presentation (higher dose of Concerta for better coverage at the beginning of the day vs. higher dose of Metadate CD or Ritalin LA for better coverage at the end of the day).

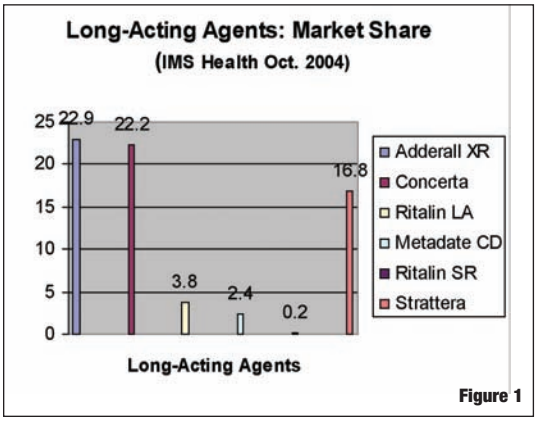


Figure 1

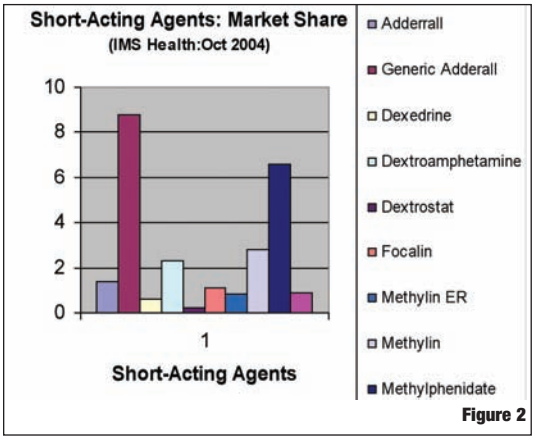


Figure 2

There are no comparative studies to guide us regarding Adderall XR and Dexedrine Spansules. If optimal response is not obtained with the initial drug chosen, trials of the other preparations should be considered.

It is important to note that the long-term agents are not new drugs, but the same compounds using different delivery mechanisms. The benefit of these new preparations is

their extended duration of action. This is not a new finding given that this was shown with Dexedrine Spansules in 1990,[36] but marketing of the recently developed drugs has informed providers and consumers of this benefit. Short-acting preparations still play a vital role. They are frequently used on weekends or holidays when full-day coverage isn't needed. Since adverse effects are dose dependent, short-acting preparations can minimize these negative effects (e.g., appetite suppression).

Long-term studies of the short-acting preparations show persistence of treatment efficacy over 2 to 5 years.[53,81] Long-term data on these long-acting agents are being gathered.

Strattera is the new compound in treating ADHD. It is effective, but comparative studies with stimulants are showing what we have been observing clinically—for many children it doesn't work as well. Clinically, we also have observed a small group of children who have a preferential response to atomoxetine, and this appears to be supported by Newcorn's findings where 51 percent of methylphenidate non-responders improved with atomoxetine.[50] The stimulants also are formidable competitors with regard to adverse events given their safety record over decades of use. After two years of clinical use, atomoxetine appears to be well tolerated; however, recent reports of two cases of hepatotoxicity raise concern. If hepatotoxicity is found to be more than a rare idiosyncratic event, atomoxetine may have more limited use.

In the future, an individual's unique pharmacogenetic data that considers pathophysiological and metabolic characteristics may allow targeted treatment that may maximize optimal response and minimize adverse effects.

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